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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,795	07/09/2003	Andrew J. Dannenberg	CRF D-2756 NB	8535

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EXAMINER	
ROBERTS, LEZAH	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/614,795	DANNENBERG ET AL.	
	Examiner	Art Unit	
	Lezah W. Roberts	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-5 is/are pending in the application.

4a) Of the above claim(s) 3-5 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-2 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 07 Oct 2003.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-2, drawn to a method of screening an inhibitor, classified in class 435 and 424, subclass 4 plus and 9 plus respectively.

II. Claims 3-5, drawn to a method of treating a patient with an inhibitor, classified in class 514, subclass 1 plus.

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions refer to a method of screening a COX-2 inhibitor and a method for using a COX-2 inhibitor that was screened by the first method. These methods steps are not related. One method tests the function of the inhibitor in vitro and the second method deals with treating a patient with the inhibitor.

Because these inventions are unrelated for the reasons given above and have acquired a separate status in the art as shown by their different classification and are distinct for the reasons given above and the search required for Group II is not required for Group I, restriction for examination purposes as indicated is proper.

Election

Claim 2 is generic to a plurality of disclosed patentably distinct species comprising a method of screening comprising at least two of (a) activation of PPRE luciferase by at least 100%, (b) at least 50% decrease in level of or 50% downregulation of expression of Class I family of receptors tyrosine kinase, (c) at least 50% downregulation of expression of cyclin D1, (d) at least 50% downregulation of expression of HPV16 oncoproteins E6 and E7, (e) at least 50% increase in expression of PTEN, (f) at least 50% inhibition of tcf/lef/beta-catenin-mediated promoter activation, and (g) at least 50% increase in level of Nrf-2. Applicant is required under 35 U.S.C. 121 to elect two disclosed screening methods, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Eric S. Spector on August 6, 2005, a provisional election was made without traverse to prosecute the invention of Group I, claims 1-2. During another conversation with Eric S. Spector on August 22, 005, a provisional election was made for the election of species to elect group (a) and (b) of claim 2 as the screening methods of invention I. Affirmation of this election must be

made by applicant in replying to this Office action. Claims 3-5 were withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims

Rejections, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1) Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim recites a method for screening a selective inhibitor of COX-2 for functionality in addition to COX-2 protein inhibition yet the word "functionality" is not clearly defined within the specification. The applicant does not disclose what functionality encompasses or examples of such functions. It is assumed by the wording of the claim; the word "functionality" refers to how the selective COX-2 inhibitor affects a "COX protein inhibition independent therapeutic activity". The phrase "COX protein inhibition independent therapeutic activity" is defined as "therapeutic activity unrelated to the inhibition of prostaglandin synthesis" (page 3, lines 7-9). The applicant describes select COX protein inhibition independent therapeutic activities as recited in claim 2 but does not adequately disclose a representation of all

the possible "COX protein inhibition independent therapeutic activities" that can possibly be screened (a potentially almost infinite set of possibilities).

2) Claim 2a recites a method of screening which comprises screening for activation of PPRE-luciferase by at least 100 %, which is a result but is not a therapeutic function. The claim indicates the method is to screen for a "COX-2 protein inhibition independent therapeutic function". The claim does not clearly convey what function or therapeutic activity is being measured by monitoring PPRE-luciferase activity. The claim reads as if the activation of PPRE-luciferase is the therapeutic activity, which is not supported by the specification. Although the applicant discloses "the ability of a test compound to stimulate PPRE-luciferase signifies that the test compound activates PPAR-mediated gene transcription", this does not support the claim as written. It also does disclose measuring PPAR activity by luciferase assay but no other assays. It is concluded that activation refers to PPRE-luciferase and not PPAR-mediated gene transcription activation. The applicant also discloses activation by 100% but does not disclose if this refers to a 100% decrease or increase in luciferase activity. It is concluded any change in luciferase activity by 100 % is considered activation of luciferase activity.

Rejections, Anticipation

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Vadlamudi *et al.*

Vadlamudi et al. discloses the effect of a selective inhibitor of cyclooxygenase-2 (COX-2), NS-398, on neu-differentiation factor-beta (NDF) -mediated growth stimulation of LS174T cells. The results showed NS-398 inhibited NDF-induced increased cell growth in LS174T cells (page 311, column 1). The amount of PGE2 was also measured showing the production of PGE2 was also decreased (page 311, column 1). This method can be used to screen selective COX-2 inhibitors as recited in claim 1 because NDF is independent of COX-2 protein inhibition. The reference also discloses there are increased levels of COX-2 in colorectal adenocarcinomas compared to adjacent normal-appearing mucosa and inhibition of the COX-2 enzyme by specific COX-2 inhibitors reduces tumor formation and regresses pre-existing tumors.

Rejection, Obviousness

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Winde et al. in view of Subbaramaiah et al.

Winde et al. discloses a COX-2 inhibitor, sulindac decreased HER-2 expression in rectal mucosa familial adenomatous polyposis patients (FAP) (see abstract). The HER-2 protein is overexpressed in breast, gastric, and colon cancer (page 201, column 2). A chemopreventive study was conducted to elucidate the possible influence of sulindac on an oncogenic tyrosine kinase receptor (HER-2) by comparing the HER-2 expression in rectal mucosa of FAP patients undergoing treatment with sulindac with those of several control groups. The control groups included a group of FAP patients that were not treated with sulindac, healthy patients, patients with Crohn's disease and a group of patients with rectal cancer. The FAP control group had a mean HER-2 level of 1639 fm/ml with a confidence interval (CI) of 1155-2122 fm/ml. The sulindac treated group had a mean HER-2 level of 503 fm/ml and a CI of 293-713 after 3 months of low-dose sulindac treatment (page 203, column 2). These values represent a more than 50% decrease in HER-2 levels as recited in claim 2b. The reference differs form the

instant claim insofar as to not disclose measuring for COX protein inhibition independent therapeutic activities a, and c-g.

Subbaramaiah et al. disclosed COX-2 is overexpressed in transformed cells and in malignant tumors. Luciferase-DNA constructs were used to determine the effect of COX-2 inhibitors, PPARγ ligands, on COX-2 promoter activity. Luciferase activity was measured to determine promoter activation in the presence of the PPARγ ligands. When promoter activity was induced by phorbol 12-myristate 13-acetate (PMA), the PPARγ ligands decreased promoter activity by more than half at concentrations above 20 μM. When PMA was not present, promoter activity was increased by more than 100 % in the presence of the ligands. The reference differs form the instant claim insofar as to not disclose measuring for COX protein inhibition independent therapeutic activities b-g.

It would have been obvious to one of ordinary skill in the art to have combined the measuring of HER-2 in the presence of a COX-2 inhibitor of the primary reference with the measuring of the luciferase activity in the presence of a COX-2 inhibitor of the secondary reference motivated by the desire to determine whether the selective COX-2 inhibitor downregulates HER-2 in cancer cells where COX-2 and HER-2 are overexpressed as well as determine if the inhibitor is stopping the overexpression of the COX-2 inhibitor by stopping promoter activity or protein inhibition as disclosed by the secondary reference. By knowing the outcome of these screening techniques, in diseases such as colorectal cancer, therapeutic functions can be treated with one agent as oppose to two as well as possible treatment with a lower amount of inhibitor needed to treat COX-2 overexpression.

Claims 1-2 are rejected.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lezah W. Roberts whose telephone number is 571-272-1071. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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